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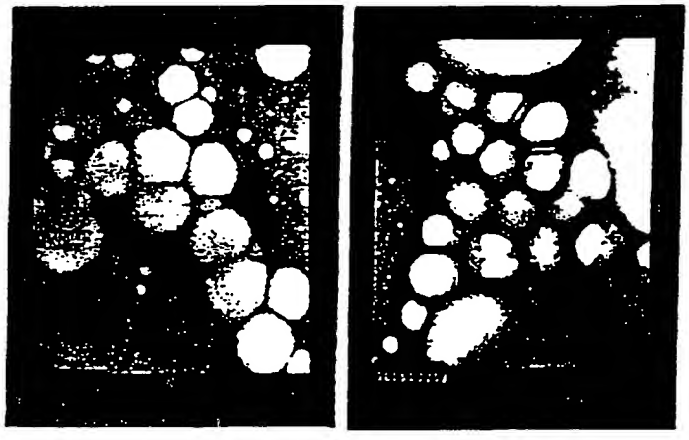
(54) PROCESS FOR COATING DROPLETS OR NANOMETRIC PARTICLES

(57) The process comprises: (1) preparing a fine dispersion of droplets or particles which contain or are formed of a chemical or biologically active substance in a phase comprised of a solvent and a non solvent of the polymer forming the coating and optionally a surfactant or suspensor agent; (2) preparing a phase which contains the coat-forming polymer dissolved in a miscible solvent in any proportion with the prior dispersion; (3) mixing both phases continuously while maintaining constant the relationship between the phases and the mixture volume and simultaneously spraying the resultant mixture in an evaporation system with temperature and vacuum conditions which provide for the instantaneous evaporation of the solvent from the polymer, causing the deposition of the polymer around the particles or droplets. Application to pharmacy, medecine, cosmetics, veterinary, chemical industry, agriculture, etc.



A B

FIG.1

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Description

TECHNICAL FIELD OF THE INVENTION

The present invention is comprised within the technical field of microencapsulation, particularly, in the coating of droplets or particles with sizes comprised within the nonometric range, using biodegradable and biocompatible polymers of different nature. The thus obtained products have important applications in pharmacy, medicine, cosmetics, veterinary, chemical industry, agriculture etc.

STATE OF THE ART

The obtention of a fine suspension of particles formed by a biodegradable polymer, the polycaprolactone, by means of precipitation due to a change of solvent, already appears described in the cientific work "Mechanism of the biodegradation of polycaprolactone" (1983), Jarret, P. et al. Polum Prep. (Am. Chem. Soc. div. Polum. Chem.) Vol. 24 No. 1, page. 32-33.

Patent EP 0274961B1 (which corresponds to U.S. Patent No. 5049322) describes a method for the obtention of vesicular type, spherical particles with size below 500 nm. The method coomprises the preparation of a phase containing a polymer, an oil and a substance to be encapsuled in a solution or dispersion. Said phase is added, under agitation to another phase formed by a non solvent of the polymer and of the oil, producing the precipitation of the polymer and subsequently the elimination of the solvents by lyophilization. On incorporation of one phase over another, the size of the reactor which contains the mixture is to be increased depending on the final volume desired. This implies the necessity of a scaling to adapt the manufacturing conditions. There exists the difficulty in large volumes in that, once the mixture is formed, the polymer solvent must be in contact with the nanocapsules during a long period, with the possibility of producing the redisolution of the same, or the exit of the active substance to the external phase. On the other hand, the elimination of solvents by means of lyophilization is a slow and expensive process, with the additionl disadvantage that when inflammable solvents are involved, it is highly dangerous.

The present invention intends the coating of already formed droplets or particles, due to which it is not necessary to agitate the mixture, which is effected by incorporation of the two phases in a device in which the mixture flows continuously, with the immediate production of the evaporation of the solvents. The elaboration and facility conditions (reaction volume) is always the same, independently of the final volume to be obtained, due to which it does not require scaling for the obtention of industrial quantities. The solvent remains in contact with the recently coated vesicules during a very short period, so that the redisolution of the coating and the possible exit of the active principle to the external phase is avoided, whatever the volume to be prepared.

The process described in FR A2 515960 allows the obtention of polyalkylcyanoacrylate biodegradable nanocapsules, parting from the polymerization of the corresponding monomer. Said nanocapsules contain a biologically active substance. The disadvantage of this method is that it requires a polymerization stage, due to which it shall only be used with specific polymers. Besides this important limitation, it involves the difficulty of having to keep a control of the polymerization and the possible existance of residual monomers which may, in some cases, be toxic. The present invention has the advantage that it does not require a polymerization, being a more rapid process and being applicable to a great number of polymers of diverse nature.

The process described in EP 0480 729 A1 consists of the coating of droplets in oil, containing active principles for oral administration, with a polysaccharide with chelator capacity (sodium alginate) which hardens on the addition of multiple-valued cations, with the result thereof, of microcapsules with sizes over 1µm. Finally, it is lyophilized to obtain a product in powder form. This method is limited to the employment of polysaccharides with chelator capacity. Likewise, sonication is necessary, not being applicable for those active substances which are degraded by ultrasonic action. Additionally, the use of a multiple-valued cation solution makes difficult its employment by any form other than orally. The present invention provides coated droplets with sizes appreciably below 1µm, does not require hardening agents, does not use sonication, and the product obtained may be administered orally, parenterally, through the nose, eyes, skin, lungs or any other form of administration.

In the process described in EP 0462003 A1 microcapsules, with sizes comprised within 25 and 100 µm with oil inside, are obtained when dried by atomization and oil/water emulsion formed by the active principal and a gastroresistant polymer acquose solution, producing a fine powder, by means of the use of an atomizer at a temperature of 140°C. The use of high temperatures is a disadvantage since it limits the use of this method when the substance to encapsule is thermosensitive. This method is only usable for water solube polymers and additionally differs from the object of the present invention in that the sizes obtained are much greater.

The process described in EP 0556917 A1 allows the obtention of biodegradable microcapsules containing an active substance parting from the ultrasonic atomization of a solution or suspension, over a non solvent, in such a way that the coagulated droplets are transferred to a second non solvent. This method, besides being complicated and requiring various solvents and a special atomizer by sonication, only allows the obtention of microcapsules with sizes over 10 µm.

Unlike all previously mentioned patents, the present invention is a method which allows the obtention of great quantities of the product without changing the conditions or facilities, and consequently, to easy industrialize. This method allows the rapid and continuous coating of temperature or sonication sensitive active substances, resulting in a final product which is usable in any field, specially in the pharmacy and veterinary field.

DESCRIPTION OF THE INVENTION

The present invention refers to a new process for the coating of droplets or particles with sizes below a micrometer, which contain, or are formed, of one or various chemical or biologically active substances. In consequence, the present invention allows the obtention of particles or droplets coated by one or various biodegradable and/or biocompatible polymers with diameters comprised within 100 and 1000 nm, preferably within 200 and 500 nm.

For the performance of the present invention, a fine dispersion of droplets or particles is prepared. In the case of dealing with droplets, the active substance is dissolved in a lipidic substance (generally an oil) or in a substance at fusion point below the temperature of the dispersing means. The droplets may also be constituted by the actual active substance. When dealing with solid particles, these may be the actual active substance. When dealing with solid particules, these may be the actual active substance or have the active substance dispersed inside. They may also be part of a microorganism or integral microorganisms with sizes below one micrometer. The dispersing phase is constituted by a solvent and a non solvent of the polymer which forms the coating and, optionally, contains one or more surfactant or suspensor agents (PHASE 1). The relationship between the solvent and the non solvent in PHASE 1 must be the adequate one, so that the coat-forming polymer does not precipitate when mixed with the phase which contains the polymer. The phase which contains the coat-forming polymer (PHASE 2) is prepared by disolving the coat-forming polymer in a solvent equal to the one used as part of PHASE 1, or any other which is miscible in a high relationship with the solvent of the polymer used in PHASE 1.

Once PHASE 1 and PHASE 2 have been separately prepared, they are lead through separate tubes to a mixing zone, where they are made to contact continuously, without agitation or ultrasonics, keeping their relationship constant (that which avoids the instantaneous precipitation of the polymer) and the volume of the mixture. During the mixing, the polymer shall not deposit on the droplets or particles, though the deposition process may be initiated, which occurs instantaneously when the mixture is pulverized in an evaporation system with temperature and vacuum conditions allowing the rapid evaporation of the polymer solvent, which provides for the immediate deposition of the polymer around the droplets or particles. Optionally, part of the non solvent, or the totality of the same, may be eliminated until a concentrated or dry product is obtained.

The conduction of the phases towards the mixture device zone, may be carried out by means of any pumping system, or with the help of pressure or vacuum.

It is a characteristic of this process that, once PHASE 1 and PHASE 2 have been prepared, the formation of the mixture, the pulverization of the mixture and the deposition of the polymer are carried out in a totally continuous and sumultaneous manner in time.

The relation between the solvent and the non solvent of the coat-forming polymer in the initial dispersion must be the adequate one, so that when in contact with the phase which contains the polymer in the solution, the immediate deposition of the polymer is not produced. In the case when the polymer tends to precipitate in the mixture of the phases, the small dimensions of the mixing zone allows the entrance of the phases in the mixing zone, and their exit in the form of powder through the other end is so rapid, that the polymer has no time to precipitate. In this way, an uncontrolled precipitation is avoided which would produce the formation of aggregates, and it ensures that the coating is produced at the moment of pulverization or nebulization.

The selection of the solvent and the non solvent of the polymer in the initial dispersion, is carried out depending on the chemical and physico-chemical characteristics of the polymer, or the oil or lipidic substance, and of the active substance to be incorporated.

If the coat-forming polymer is non soluble in water, the non solvent may be a more or less complex aqueous solution, and the solvent may be any organic solvent which is miscible with a high relationship in water, capable of disolving the polymer. The solvent of the polymer may be for instance, an alcohol such as ethanol, methanol, isopropanol, a ketone of low molecular weight such as acetone or methyl ethyl ketone or any other solvent such as acetonitrile or the tetrahydrofuran. Normally, the solvent of the polymer has a dielectric constant over 15.

In the case that the polymer be soluble in an organic solvent and water soluble depending on the pH or temperature, the aqueous solution of the inicial dispersion must adjust to a pH and/or temperature at which said polymer be insoluble to ensure the deposition of the polymer when the evaporation of the solvent is produced during the pulverization.

The lipidic substance to be dispersed in the water may be a natural oil such as coconut oil, soya oil, olive oil, castor-oil, a mixture of capric acid tristearates and capric acid with glycerol, a mixture of saturated and unsaturated acid fats C_{12}-C_{18} where the main constituyent is the linolenic acid (48%), a mixture of unsaturated polyglycosided glycols constituted by glycerols and polyethyleneglycol esters, a mixture of saturated polyglycosided C_8-C_{10} glycerols, a palmita-

teester of glycerol formed by mono, di and triglycerols of natural C_{16} and C_{18} fat acids or a mixture of the same, a mineral oil or a phospholipid.

Generally, the concentration of the lipidic substance in the final product is comprised within 0,1 and 10% (p/V), preferably within 0.5 and 5% (p/V).

The surfactant or emulgent agent of PHASE 1 may be amphoteric such as soya or egg lecitine, anionic such as sodium laurylsulfate, cationic such as benzalkonium chloride or non ionic such as sorbitane mono oleate, sorbitane monoestearate, a polysorbate or a copolymer of polyoxyethylene-polyoxypropylene or a mixture of the same.

The suspensor agent may be a dextran, polyvinylic alcohol, a celulosic derivate or a natural rubber such as xanthane rubber. Any of these may be used combined with a surfactant agent of the ones previously mentioned.

The surfactant or suspensor agent concentration in the final formula es comprised within 0.01 and 10% p/V).

In PHASE 2, the polymer used may be a synthetic polymer such as the glycols derived from propiolactone, butyrolactone and the epsilocaprolactone; a hemisynthetic polymer such as celulose acetobutyrate, ethylcelulose, hydroxypropylmethylcelulose acetophtalate; the acrylic acid copolymers and the acrylic polymer, lactic acid copolymers with the glycol acid or the polycaprolactone. Other polymers which may be employed are the celulose acetophtalate, the polyanhydrids, the polyalphahydroxyacids and the natural polymers.

The concentration of the coat-forming polymer in the organic phase is comprised within 0.01 and 5% (p/ V).

Different forms of mixing the two phases exist. It may be performed through two parallel tubes, producing the union in a concentric or "Y" shaped zone, in such a way that the two phases are joined simultaneously. The volumes of the phases may be equal or the volume of one phase may be greater as regards the other. The mixing zone has, on the extreme end at which the phases are incorporated, a suitable device, so that the mixture exits in powder form towards an evaporation system in which the solvent of the polymer is totally eliminated and optionally part of, or the whole of the non solvent under reduced pressure and at a temperature below 50°C. The degree of vacuum and the temperature must be adjusted depending on the solvent of the polymer used. In this way, the rapid evaporation of the solvent and the immediate deposition of the polymer around the droplets or particules is ensured, and the formation of aggregates or the appearance of uncoated particles or droplets is avoided.

The product thus obtained may be used in suspension or dry powder form, be extruded, compressed or granulated and be used alone or forming part of a more complex blend.

An analysis is subsequently carried out of the experimental results obtained in some specific tests performed according to the process of the present invention.

1. Nanoemulsion coating tests without drug

In order to study the suitability of the process for coating droplets, which is the object of the present invention, various formulations are prepared with the purpose of checking that the polymer is mainly deposited around the oil droplets instead of individually precipitating in the form of nanospheres, the greater part of the oil droplets remaining uncoated. For this, the three types of products which could be formed, were separately prepared: nanocapsules, naoemulsions and nanospheres.

a) A nanoemulsion of a mixture of caprylic acid and caprynic acid triesters with polyepsyloncaprolactone coated glycol, was prepared according to the process specified in the description of the present invention.

b) A nanoemulsión mixture of the caprylic acid and caprynic acid triester with glycol was prepared in the same manner as in previous section (a), but without adding polymer in the organic soluciton (PHASE 2) of the description of the present invention.

c) For the obtention of nanospheres, the process detailed in the description of the present invention was followed, but only using a mixture of solvents and non solvents of the coat-forming polymer (polyepsyloncaprolactone), without oil, as PHASE 1.

A determination was made of the particle size, the polydispersity and the Z potential of the resultant products of (a), (b) and (c) with a Zetasizer 3 (Malvern Instruments England).

As may be observed in Table 1, the values of the average size and the polydispersity of the uncoated oil droplets are greater than those of the coated oil droplets and these, in turn, are greater than the nanosphers.

The Z potential (parameter which gives an idea of the electric load on the surface of the droplets and particles), is -18mV for coated droplets, while for the free oil droplets it is -8mV and for the nanosphers it is -14mV.

Table I

	Non ionic Surfactant final% (p/V)	Poly caprolac-tone final% (p/V)	Oil Final% (p/V)	Average size (nm)	Poly dispersity	Z potential (mV)
NC	2.5	1.25	2.5	192	0.150	-18
NE	2.5	-	2.5	307	0.302	-8
NS	2.5	1.25	-	149	0.022	-14
NC: coated nanoemulsion; NE: nanoemulsion; NS: nanospheres.						

The values of size, polydispersity and Z potential correspond to the average of 10 measurements.

An evaluation was conducted, by means of electronic microscopy at transmission of 66.000 magnification on diverse samples of the resultant products of (a) and (b) which were previously tinted with uranyl acetate at 1%.

As can be observed in figure 1, the uncoated oil droplets (A), appear as uniform particles which adapt with one another, while coated oil droplets (B) appear as particles with a less dense core, surrounded by a transparent zone limited by a dark edge (polymeric coating).

2. Nanoemulsion coating test with drug

The proceedings were similar to the previous section for the formulations without active principle, and a mixture of nanoemulsion and nanosphere was additionally prepared.

a) A nanoemulsión of a mixture of caprylic acid and caprinic acid triesters was prepared with polycaprolactone coated glycol, containing indometacine at 0.1% (p/V) according the the process detailed in the description of the present invention.

b) A nanoemulsión of a mixture of caprylic acid and caprynic acid triesters was prepared with glycol containing indometacine at 0.1% (p/V) in the same manner as in previous section (a) but without adding polyepsyloncaprolactone in the organic solution PHASE 2 of the description of the present ivnention.

c) For the obtention of indometacine nanospheres at 0.1% (p/V), the process detailed in the description of the present invention was followed, but only using a mixture of solvent and non solvent of the coat-forming polymer (polyepsyloncaprolactone), without oil, as in PHASE 1.

Additionally, a dispersion of oil droplets and nanoparticles was prepared, mixing at equal parts, the resultant products of previous sections (b) and (c)

A determination was made of the size of particle, the polydispersity and the Z potential with a Zetasizer 3 (Malvern Instruments, England), and 5 ml of each one of the products was centrifuged during 2 cycles of 1h at 4000 rpm in a centrifugal Selecta model Centromix.

The results are represented in Table II and in Figure 2. As may be observed in Table II, the average size values and the polydispersity values of the uncoated oil droplets are greater than those of the coated oil droplets and these, in turn, are greater than those of the nanospheres. The average size and the polydispersity of the nanosphere mixture and the uncoated oil droplets give intermediate values to those corresponding to the separate products and greater than those obtained for the coated droplets. Likewise, the nanosphere and nanoemulsion mixture showed a bimodal distribution (two populations of particle sizes). As regards the Z potential, the values obtained for the mixture of the nanospheres and the uncoated oil droplets, are comprised within the values corresponding to each product separately.

The Z potential of the coated droplets is greater (in absolute values) to those of the nanospheres, to the uncoated droplets and to their mixture. Consequently, the product obtained by the process which is the object of the present invention, is not the result of a mixture of precipitated polymer particles (nanospheres) and of uncoated oil droplets.

Table II

	Non-ionic surfactant final%	Polycaprolactone final% (p/V)	oil final% (p/V)	Indometacine final% (p/V)	Average size (nm)	Polidis.	Z Pot. (mV)
NC	2.5	1.25	2.5	0.1	419	0.157	-38
NE	2.5	-	2.5	0.1	1026	0.319	-24
NS	2.5	1.25	-	0.1	345	0.121	-36
NS+NE	2.5	1.25	2.5	0.1	511	0.199	-31
NC: coated nanoemulsión; NE: nanoemulsión; NS: nanoespheres; NS+NE: mixture at equal parts of nanospheres and nanoemulsions.							

The values of size, polydispersity and Z potential correspond to the average of 10 measurements.

As may be observed in Figure 2, the nanospheres (NS) show a white sediment at the bottom of the tube, while the nanoemulsión (NE) shows a whitish float. On its part, the nanosphere and nanoemulsión mixture (NS+NE) presents at the same time, a sediment and a floating, besides a practically transparent intermediate liquid. On the other hand, the coated oil droplets (NC) show a minimum sediment and floating but the intermediate liquid is much cloudier (whitish). This intermediate coat, which is wider and cloudier, would correspond to the coated oil droplets with an intermediate density between that of the one corresponding to the oil droplets (less dense) and those of the nanospheres (denser).

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: (A) represents uncoated oil droplets which appear as uniform particles which adapt with one another; (B) represents the coated oil droplets which appear as particles with a denser core, surrounded by a transparent zone limited by a dark edge, (polymeric coat).

Figure 2 : Is a comparison of the appearance of the intermediate liquid in test 2, between the nanospheres (NS), the nanoemulsión (NE), the mixture of nanospheres and nanoemulsion (NS+NE) and the coated oil droplets (NC).

EMBODIMENTS OF THE INVENTION

The present invention is additionally illustrated by means of the following examples, which must not be considered as limitative of the scope of the same, and which is defined by the attached note of the claims:

For the description of the examples, the commercial names of the products are used, which must be understood to be any product with the same characteristics, commercialized by any other Company. The products are as follows:

Miglyol 812® (Dynamit Nobel, Sweden): is a mixture of caprilic acid triesters and caprinic acid with glycol.

Edenor TiO_2 (Henkel, Dusseldorf): is a mixture of saturated and unsaturated fat acids C_{12}-C_{18} where the main constituyent is the linolenic acid (48 %)

Eudragit L 12 5 P Rohm Pharma, Darmstadt): is a polymerizied anionic of the metacrylic acid and methyl metacrylate.

Lutrol F68 (BASF, Germany): is the Poloxamer 188 which is a copolymer of polyoxyethylene and polyoxypropylene.

EXAMPLE I
NANOEMULSION OF MIGLYOL 812® COATED WITH POLYEPSILON CAPROLACTONE

0.625 g of Lutrol F 68® is dissolved, under agitation, in 62 ml of deionized water and filtered through 0.22 µm. 0.625 g of Miglyol 812® is dissolved in 62 ml of acetone. The acetonic solution is incorporated to the initial acquose solution under magnetic agitation, so that a dispersion of droplets with average size below 1µm is obtained (Phase 1). 0.312 g of polyepsyloncaprolactone is dissolved in 125 ml of acetone with the help of ultrasonics (Phase 2). The two phases are continuously mixed through the two parallel tubes, maintaining the relation of the phases constant in the mixing zone and pulverizing the resultant mixture towards the evaporation system simultaneously to the formation of the mixture. In the evaporation system eliminate, under reduced pressure and at a maximum temperature of 45ºC, the acetone (polymer solvent) so that the deposition of the polymer around the oil droplets is produced and eliminate part of the water (non-solvent of the polymer) until a final volume of 25 ml is reached. The average size of the coated droplets, measured in a Zetasizer 3 (Malvern Instruments) was 192 ±0.1 nm.

EXAMPLE 2

NANOEMULSION OF MIGLYOL 812® COATED WITH POLYEP SILONCAPROLACTONE

Follow the technique described in Example 1, but the ratio of solvents in the initial dispersion is of 2:3 water/acetone expressed in volumes, instead of 1:1 water/acetone. The average size of the coated droplets, measured in a Zetasizer 3 (Malvern Instruments) was of 307 ± 0.5 nm.

EXAMPLE 3

NANOEMULSION OF MIGLYOL 84 0® COATED WITH POLYLACTICGLYCOLIC COPOLIMER 75:25

The technique described in example 1 is followed, but using 0.830g of Lutrol F68®, 0.207g of polylactic-glycolic copolymer instead of polyepsiloncaprolactone and 0.415g of Miglyol 812®. The average size of the coated droplets, measured in a Zetasizer 3 (Malvern Instruemnts) was of 197 ±5nm.

EXAMPLE 4

NANOEMULSION OF CARTEOLOL BASE AT 0.2% COATED WITH POLYEPSILONCAPROLACTONE

0.375g of Lutrol F68®is dissolved in 40ml of deionized water and filtered through 0.22µm under agitation. 0.030g of carteolol base is dissolved in 0.375g of Edenor $Ti0_s$® and the resultant solution is added to 60ml of acetone. The acetonic solution is incorporated to the initial aqueous solution under magnetic agitation, to obtain a dispersion of droplets with average size below 1µm (Phase 1). 0.187g of polyepsiloncaprolactone is dissolved in 100ml of acetone with the help of ultrasonics. (Phase 2). The two phases are continuously mixed through the two parallel tubes, maintaining the ratio of the phases constant in the mixing zone, and pulverizing the resultant mixture towards the evaporation system simultaneously with the formation of the mixture. In the evaporation system, the acetone is eliminated (solvent of the polymer), under reduced pressure and at a maximum temperature of 45ºC, so that the deposition of the polymer around the oil droplets is produced and part of the water is eliminated (non solvent of the polymer) until a final volume of 25ml is reached. The average size of the coated droplets, measured in a Zetasizer 3 (Malvern Insruemnts) was of 375±3nm.

For separating the coated droplets of the external aqueous phase, the ultrafiltering-centrifugal technique was used, determining, by means of HPLC, the concentration of carteolol in the total formula and in the filtration. The percentage of the encapsulation of the carteolol was calculated by the difference between the concentration in the total formula and that of the filtration. The percentage of encapsulation was of 70%.

EXAMPLE 5

NANOEMULSION OF INDOMETACINE AT 0.1% COATED WITH POLYEPSILONCAPROLACTONE.

1.66g of Lutrol F68® was dissolved in 100ml of deionized water and filtered through 0.22µm under agitation, 0.050g of indometacine was dissolved in 0.830g of Miglyol 812® applying heat, and the resultant solution is added to 100ml of acetone. The acetonic solution is incorporated to the initial aqueous solution under magnetic agitation, so as to obtain a dispersion of droplets with average size below 1µm (Phase 1), 0.415g of polyepsiloncaprolactone is dissolved in 200ml of acetone with the help of ultrasonics (Phase 2). The two phases are mixed continuously through the two parallel tubes, maintaining the ratio of the phases constant in the mixing zone and pulverizing the resultant mixture towards the evaporation system simultaneously with the formation of the mixture. In the evaporation system the acetone is eliminated (solvent of the polymer), under reduced pressure and at a maximum temperature of 45ºC, so that the deposition of the polymer around the oil droplets is produced and part of the water is eliminated (non solvent of the polymer) until a final volume of 50ml is reached. The final pH is adjusted to 5.5 with H C1 0.1 M. The average size of the coated droplets, measured in a Zetasizer 3 (Malvern Instruments) was of 551 ±15nm.

For the separation of the coated droplets of the external aqueous phase, the ultrafiltering-centrigugal technique was used, determining by means of HPLC, the concentration of indometacine in the total formula and in the filtration. The percentage of encapsulation of the indometacine was calculated by the difference between the concentration in the total formula and that of the filtering. The percentage of encapsulation was of 99%.

EXAMPLE 6

NANOEMULSION OF MIGLYOL 840® COATED WITH EUDRAGIT L 12.5 P®

0.375G of Lutrol F68® was dissolved, under agitation in 40ml of deionized water and filtered through 0.22µm. The pH was adjusted to 4.5 with HC1 0.1M 0.375g of Miglyol 840® was dissolved in 60 ml of acetone. The acetonic solution was incorporated to the initial aqueous solution under magnetic agitation, so that a dispersion of droplets with average size below 1 µm was obtained. (Phase 1). 0.150 g of Eudragit L 12.5 P® was dissolved in 100 ml of acetone (Phase 2). The two phases are continuously mixed through the two parallel tubes, maintaining constant the ratio of phases in the

mixing zone and pulverizing the resultant mixture towards the evaporation system simultaneously with the formation of the mixture. In the evaporation system, the acetone (solvent of the polymer) is eliminated under reduced pressure and at a maximum temperature of 45ºC, so that the deposition of the polymer around the oil droplets is produced and part of the water (non solvent of the polymer) is eliminated, until a final volume of 15ml is reached. The average size of the coated droplets, measured in a Zetasizer 3 (Malvern Instruments) was of 832 ± nm.

EXAMPLE 7
NANOEMULSION OF CARTEOLOL AT 0.1% COATED WITH EUDRAGIT L 12.5 P®

The technique described in example 6 is followed, but substituting the Miglyol 840® by Edenor TiO_8®, and 0.030 g of carteolol base was included in the oil. The average size of the coated droplets measured in a Zetasizer 3 (Malvern Instruemnts) was of 290 ± 12nm.

For the separation of the caoted droplets of the external aqueous phase, the ultrafiltering-centrifugal technique was used, determining, by means of HPLC, the carteolol concentration in the total formula and in the filtration. The percentage of encapsulation of the carteolol was calculated by the difference between the concentration in the total formula and that of the filtration. The percentage of encapsulation was of 66%.

EXAMPLE 8
POLYSTYRENE LATEX COATED WITH POLYEPSILONCAPROLACTONE

0.125g of Lutrol F68® was dissolved, under agitation, in 40 ml of deionized water and filtered through 0.22µm. To the previous solution was added 100 µm of polystyrene latex with an average particle size of 200nm and a Z potential of -30.81 mV measured in a Zetasizer 3 (Malvern Instruments) and subsequently 20 ml of acetone are added, to obtain a dispersion of droplets with average size below 1µm (Phase 1). 0.01g of polyepsiloncaprolactone is dissolved, by means of ultrasonics, in 25ml of acetone (Phase 2) The two phases are continuously mixed through the two parallel tubes, maintaining the relationship of the phases constant in the mixing zone and pulverizing the resultant mixture towards the evaporation system simultaneously with the formation of the mixture. In the evaporation system the acetone (solvent of the polymer) is eliminated under reduced pressure and at a maximum temperature of 45°C, in order to produce the deposition of the polymer around the latex particles and part of the water (not the solvent of the polymer) is eliminated until a final volume of 7ml is reached. The average size of the coated droplets, measured in a Zetasizer 3 (Malvern Instruments) was of 28 6 ± 1.5mV.

EXAMPLE 9
POYSTYRENE LATEX COATED WITH EUDRAGIT L 12.5 P

The same procedure as for example 8 is followd, but replacing the polyepsiloncaprolactone by Eudragit L 12.5 P. The initial solution of water and Lutrol F68 was adjusted to approximately pH 4. The average size of the coated droplets, measured in a Zetasizer 3 (Malvern Instruments), was of 270 ± 12nm and the Z potential of - 17.39 ± 1.5 mV.

Claims

1. Procedure for the coating of droplets or solid particles with sizes below 1 µm, which contain or are formed by a chemical or biologically active substance and with the coating formed by one or more biocompatible polymers, characterized by: preparing a phase constituted by a fine dispersion of droplets or solid particles in a solution which is formed by a solvent and a non solvent of the polymer forming the coating, containing a surfactant or suspensor agent, preparing a second phase which contains the polymer or the mixture of polymers dissolved in a solvent or in a mixture of miscible solvents in any relationship with the mixture of solvent and non solvent of the first phase, mixing without agitating and in a continuous way, the two previous phases, maintaining constant the relationship between the phases and the total volume of the mixture and spraying simultaneously, the resultant mixture towards an evaporation system where it is introduced in powder form, eliminating under reduced pressure, the adequate proportion of solvents so that the polymer is deposited around the droplets or particles and optionally, eliminate part or all of the non solvents of the polymer to obtain a concentrated or dry product.

2. Procedure according to claim 1, characterized in that the average diameter of the coated particles or droplets is below 1 µm.

3. Procedure according to claims 1 or 2, characterized in that the polymer forming the coating is biodegradable and/or biocompatible.

4. Procedure according to claims 1 to 3, characterized in that the active substance is a drug, a forerunner of a drug or a cosmetic substance.

5. Procedure according to claims 1 to 3, characterized in that the active substance is a biologically active product or a microorganism or fragments of microorganisms.

6. Procedure according to claims 1 to 5, characterized in that the active substance is dissolved or dispersed in the droplets or particles.

7. Procedure according to claims 1 to 5, characterized in that the droplets or particles are formed by the active substance.

8. Procedure according to claims 1 to 7, characterized in that the droplets are formed by an oil or lipidic substance

9. Procedure according to claims 1 to 8, characterized in that the mixing of the two phases is carried out without magnetic, mechanical or sonic agitation.

10. Procedure according to claims 1 to 9, characterized in that the mixing, the pulverization and the deposition of the polymer is carried out continuously and simultaneously in time.

11. Procedure according to claims 1 to 10, characterized in that the proportion between the solvent and the non solvent of the polymer in phase 1, allows the mixing of phases without producing the instantaneous deposition of the polymer.

12. Procedure according to claims 1 to 11, characterized in that the polymer is deposited around the droplets and particles when part of the solvent is eliminated.

13. Procedure according to claims 1 to 12, characterized in that the concentration of the surfactant agent is comprised between 0.01% and 10% (p/V).

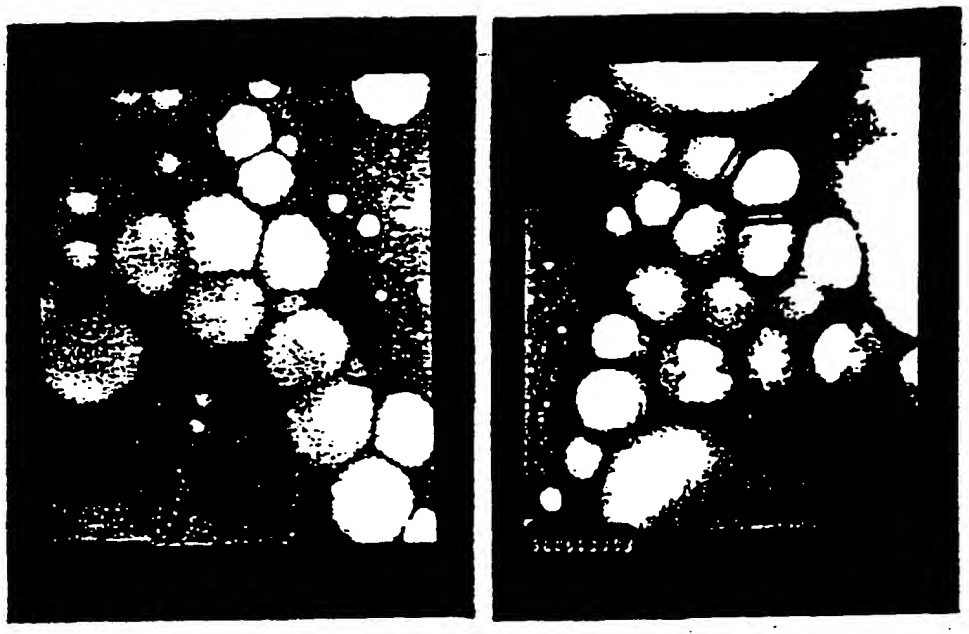
14. Procedure according to claims 1 to 12, characterized in that the concentration of the suspensor agent is comprised between 0.1% and 10% (p/V).

15. Procedure according to claims 1 to 14, characterized in that the solvents of the polymer forming the coating is miscible in the non solvents in all the proportions.

16. Procedure according to claims 1 to 15, characterized in that the solvents of the polymer forming the coating has a dielectric constant over 15.

17. Procedure according to claims 1 to 16, characterized in that the concentration of the polymer forming the coating is comprised between 0.01% and 10% (p/V).

18. Procedure according to claims 1 to 17, characterized in that the final product is lyophilized, extruded or compressed, and may be used as single component or forming part of a more complex composition.



A B

FIG.1

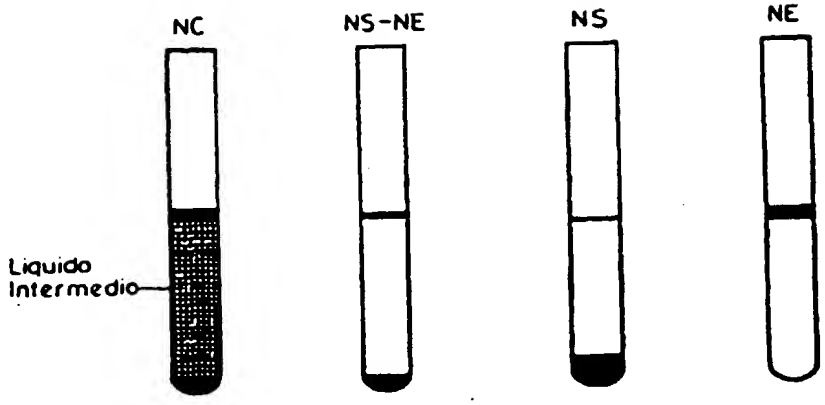


FIG.2

INTERNATIONAL SEARCH REPORT

Int. ...ional Application No
PCT/ES 94/00085

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 529 711 (LABORATORIOS CUSI, S.A.) 3 March 1993 see the whole document	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 1995	31.01.95

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ...ional Application No
PCT/ES 94/00085

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0529711	03-03-93	ES-B-	2034891	16-12-93
		DE-A-	4128910	11-02-93
		JP-A-	6057005	01-03-94

Form PCT/ISA/210 (patent family annex) (July 1992)